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[illegible] OF IMMUNITY IN ANTHRAX The effect of trauma and the significance of nervous system in the immunity in anthrax - COMMUNICATION III*

In studying the problem concerning the possibility of utilization of killed culture of Pasteurellae as the vaccinal preparation we came upon a very paradoxical phenomenon. In one case we were compelled to take a rabbit which had come out from under the experimental vaccination against anthrax for the experiment with the vaccination with killed culture of pasteurellae. This rabbit was earlier vaccinated against anthrax with the Tsenkovskii II vaccine and, as a result of the control infection with absolutely lethal dose of virulent culture of B. anthracis, it survived, which indicated the existence of a stable immunity in the animal. 28 hours after the control infection with the culture of B. anthracis the rabbit, having come out from under the experiment, was vaccinated subcutaneously with the killed culture of pasteurellae in mixture with a supplementary substance. 18 hours after the vaccination against pasteurellosis the rabbit died of anthrax.

There are analogous data in literature about the observations of S. I. Speranskii, from the laboratory of academician A.D. Speranskii,

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* Communication I. F.A. Terent'ev and E.P. Stefanova. The significance of post-vaccinal reaction in the genesis of immunity in anthrax. "Veterinariia" 10-11, 1946. Communication II. E.P. Stefanova. Vaccination of rabbits, guinea pigs and white mice with the killed culture of B. anthracis. "Veterinariia" 4, 1947.

when in a dog, which recovered from tetanus caused by a small dose of the toxin and subsequently subjected to the operation of superimposing a glass ball, the tetanic symptoms were revived soon after the operation and the dog died. In another case a rabbit, which had come out from under the experiment with the control of a series of dysenteric toxin, was taken after 22 days for another test with a poisoning substance, and in this case the typical picture of dysentery developed and the rabbit died (characteristic changes for dysentery were recorded pathologoanatomically).

S.I. Lebedinskaia notes that various irritants can cause a specific form of nervous irritation and that this specific process in the nervous system can sometimes be preserved in the latent form, but a new even if it be vulgar stimulation, acting on the nervous system, is capable of restoring this reaction in the same form.

There is information that also under the practical conditions are observed phenomena analogous to the above-cited cases. Thus, S.N. Vyshelesskii (1911) points out that in the practice of anti-anthrax inoculations of large animals, after the Tsenkovskii II vaccine, there have been observed cases of death of animals in 14-20 days after the inoculation, with the symptoms having nothing in common with anthrax. The author supposes that in these cases the vaccine served as the impetus to the development of the other infection.

These literary data and the above-described cases with the rabbit led us to the thought that B. anthracis, by virtue of some sort of causes, can be found a rather long time in the immune organism of the

rabbit and that it is capable of exhibiting its pathogenic action in the conditions of the infliction of irritation.

We carried out the following experiments in order to verify this assumption: to the rabbits, which had come out of the experiments with immunization against anthrax, after various periods following their control infection with the virus of B. anthracis, we inflicted irritation in form of a trauma - biopsy of a part of the ear. The results of these experiments are given in Table I.

TABLE I

Test series	Number of rabbits	The period in which trauma inflicted after the control infection	Result
1	7	32 days	1 died after 20 hours; B. anthracis culture isolated
2	5	26 days	1 died after 36 hours; B. anthracis culture isolated
3	6	18 days	1 died after 18 hours; B. anthracis culture isolated
4	5	15 days	2 died after 36-47 hours; B. anthracis culture isolated

As the table shows, out of 23 rabbits upon which trauma was inflicted after 15-18-26-32 days following the control infection with the virus of B. anthracis, 5 died from the anthracic sepsis.

These experiments furnish the basis to assume that B. anthracis can be preserved for a rather long time in the immune organism of rabbits, and that it is capable of causing anthracic sepsis under the influence of the ordinary operative trauma. This gives grounds to conjecture that trauma can disrupt the immune state in some vaccinated rabbits.

Taking into account what has been stated, we arranged supplementary experiments according to the following scheme. A group of rabbits was immunized against anthrax with the Tsenkovskii II vaccine, as well as with the glucoside vaccine, and then infected with the virulent culture of B. anthracis, whereupon the trauma was inflicted upon one portion of the rabbits (biopsy of a part of the ear), and the other group suffered no trauma and served as the control. The trauma was inflicted on one group of the rabbits 1 hour before and 1 hour after the infection. The data of these experiments are given in Table II.

TALLE II

Test group	With what vaccinated	No. of rabbits	Control infection			Control	
			Period after vaccination	Trauma	Result	No. of rabbits	All died after
1	Tsenkovskii II vaccine	2	3 days	No	Lived		
		2	3 days	In infection	Died after 64 120 hours	2	60-132 hours
2	Tsenkovskii II vaccine	3	5 days	No	Lived		
		3	5 days	In infection	Died after 18 24 hours		
		2	5 days	1 hour before infection	1 lived, 1 died after 24 hours	5	36-48 hours
		3	5 days	1 hour after infection	1 lived, 2 died after 24 36 hours		
3	Glucoside vaccine	3	7 days	No	Lived		
		3	7 days	In infection	1 lived, 2 died after 17 48 hours	3	64-72 hours
4	Glucoside vaccine	2	22 days	No	Lived		
		2	22 days	In infection	Died after 64 72 hours	2	48-72 hours

As is seen from the table, virtually all vaccinated rabbits on which trauma was inflicted in infection died of anthrax, while the rabbits on which trauma was not inflicted lived and had a distinctly marked immunity. The tentative experiment has shown that the infliction of trauma both 1 hour before the infection and 1 hour after the infection likewise contributes to the development of anthracic sepsis in immune rabbits.

It may be assumed on the basis of the data cited that the trauma, inflicted in infection, "remo.es" as it were the immune the immune state from the rabbits, in consequence of which they die drom anthrax. In passing, we think it necessary to bring the following fact out. In one case the rabbits which survived the experiments with the infliction of trauma were subjected to a second trauma through biopsy of the second ear 25 days after the control infection and 7 days after the first trauma. In this case too, out of 5 rabbits one died of anthrax. It is admissable that in this case the initially inflicted trauma did not produce the proper changes in the organism of the rabbit in order for the B. anthracis, which was somewhere in the organism, to exhibit its pathogenicity, while the second trauma contributed to this.

G. I. Markelov and his coworkers, in studying the influence of the vegetative nervous system on the development of infectious process and in experimenting on rabbits found that the response reaction of the organism to the infection depends in a large measure upon the status of the nervous system in general, and of the vegetative system in particular. The author points out that the specific action on the nervous system and on its

vegetative branch (surgical or chemical irritation) affects the entire course of the infectious process, and this effect is told upon both in the changes of the incubation period to the side of its reduction, and in the changes of the character of the infectious process itself to the side of its acceleration. The author notes, moreover, that the influence upon the nervous system depends not only upon the quality of the irritant and its intensity, but also upon the original status of the vegetative system, upon the number and frequency of the irritations inflicted, as well as upon the time interval between the irritation and infection of the animal.

Taking into account the data of academician A. D. Speranskii concerning the role of the nervous system in pathology, as well as the above-cited data of G. I. Markalov, we are inclined to conjecture that in our experiments the inflicted irritation, in the form of the biopsy of the ear, served as the cause not only for the reorganization of the condition of the nervous system of the organism of rabbits, but also for the reorganization, for some period of time, of their immune state. We have not yet established for what period the immune state of rabbits is "removed".

Our data, given in Table I, speak in favor of the fact that in the organism of certain rabbits which are immune to anthrax, B. anthracis can be found in the latent state. This indicates that the virus of B. anthracis in an immune organism is not always rapidly lysated under the influence of humoral factors or destroyed by phagocytes. Therefore the nature of immunity in anthrax could hardly be explained from the point of view of the cellular and humoral factors of immunity. It is fully admissible that

there are some sort of other, as yet unestablished, interrelationships of the immune organism with the virus of B. anthracis.

Proceeding from the data obtained, we arranged experiments with vegetable poisons. Through these experiments we proposed to elucidate the significance of the nervous system in the defensive reaction of the organism in anthrax.

There are in literature data to the effect that certain vegetable poisons affect the formation of antibodies and the phagocytic ability of leukocytes.

M. M. Izrael'son and Madsen, both transliterated, (1935), working with vegetable poisons, established the participation of the nervous system in the formation of antibodies.

A. N. Tordienko (1936) showed that the introduction of pilocarpine causes a 3-4 fold increase in agglutinins, while the introduction of atropine reduces the number of agglutinins in comparison with the controls.

M. V. Puchkov and G. G. Golodets (1945, 1946) note that through release of mediators into the blood, in the organism is accomplished the regulation of the phagocytic function of leukocytes, whereupon the sympathin increases the phagocytic ability and acetylcholine reduces it.

M. V. Puchkov also points out (1946) that vegetable poisons, by stimulating the release of this or that mediator, intensify or depress the phagocytosis.

The recent works of the students of academician Bogomoletz attest to the fact that there exists a close dependence of the plastic barrier and

defensive function, the so-called physiological system of the connective tissue, upon the status of the vegetative nervous system of the organism. Thus, according to their experiments adrenalin decreases the activity of the physiological system of connective tissue, while acetylcholine produces a clearly stimulating effect.

It is evident from these brief data that vegetable poisons, by influence upon the nervous system of the organism, modify its reactivity and thereby affect the formation of antitoxins, agglutinins and the phagocytic ability of leukocytes.

Taking into account the indicated literary data as well as our experiments on the effect of a painful irritation on immunity in anthrax, we carried out experiments according to the following scheme.

Groups of rabbits were immunized against anthrax with the Tsenkovskii II vaccine in 0.1cc dose and after 10 days they were infected with the absolutely fatal doses of the virus of anthrax; 30 minutes before the infection the rabbits received subcutaneously: the first group - adrenalin, second group - pilocarpine, and the third - atropine. In addition, vaccinated rabbits were taken at the same time, to which trauma was inflicted (biopsy of the ear) 30 minutes before the infection and 30 minutes after the infection. The results of these experiments are given in Table III.

TABLE III

Number of rabbits	Vaccine and dose	Control infection			
		Period after vaccination	Processing	Virus and dose	Result
2	Tsenkovskii II vaccine, 0.1cc subcutaneously	10 days	Adrenalin	Standard virus of the Control Institute, series 6, dilution 1:100 dose 1cc	Lived
2		10 days	Pilocarpine		"
2		10 days	Atropine		Died after 64-72 hours
2		10 days	Trauma 30' before infection		Died after 36-120 hours
2		10 days	Trauma 30' after infection		1 lived, 1 died after 132 hours
3	Control		None		All died after 30-60 hours

A pure culture of B. anthracis was isolated from all that died.

As is seen from the table neither adrenalin nor pilocarpine affected the immune condition of the rabbits which had been vaccinated against antrhax; they survived. But the rabbits which received atropine before the infection died.

This indicates that atropine apparently modifies for a period the immune status in rabbits, and they died equally as the controls. The same, as the table shows is observed also in the infliction of a painful irritation. Thus, out of 4 rabbits upon which trauma was inflicted 30 minutes before and 30 minutes after the infection, 3 died.

The subsequent experiments with atropine confirmed these data, which may be judged from Table IV.

TABLE IV

Number of rabbits	Vaccine and dose	Control infection			
		Period after vaccination	Processing	Virus and dose	Result
5	Tsenkovskii II vaccine,	10 days	Atropine	Standard virus of the Control	4 died, 1 lived
5	0.1cc subcutaneously	10 days	None	Institute, series 6, dilution 1:100, dose 1cc	4 lived, 1 died
2	Control		None		Both died

A pure culture of B. anthracis was isolated from all that died.

It is seen from the data cited that the rabbits, processed with atropine before the infection, die of anthracic sepsis equally as the controls. Therefore not only a painful irritation - trauma - but also the introduction of atropine into the vaccinated rabbits in infection destroys their immune state and the rabbits die of anthrax equally as the non-vaccinated rabbits.

It may be stated on the basis of these experiments that the nervous system is of extremely important significance in the immunity in anthrax.

We have pointed out above also that a portion of the rabbits which had been earlier vaccinated against anthrax and lived after the control infection, in infliction of trauma (biopsy of the ear) almost one month after the infection, died of anthrax.

The subsequent analogous experiments with the infliction of trauma, as well as the introduction of atropine into immune rabbits which lived

after the control infection, gave concurrent results, which may be seen from Table V.

TABLE V

ct series	Number of rabbits	Method of processing	Processing after control infection	Result
1	6	Trauma (biopsy of ear)	23 days	1 died of anthrax, 5 lived
2	5	Trauma	18 days	1 died of anthrax, 4 lived
3	2	Trauma	34 days	Lived
4	3	Trauma	15 days	1 died of anthrax, 2 lived
5	4	Atropine, subcutaneously	26 days	1 died of pasteurellosis, 2 died of anthrax, 1 lived

The experiments cited in Table V corroborate the earlier obtained results that the infliction of trauma causes the death from anthrax of a portion of vaccinated rabbits and of those undergoing the control infection. The same is observed also in the injection of atropine.

These experiments also show that the agent of anthrax can be found in the immune organism for about a month without exhibiting its pathogenic action. This fact of "bacillo-carriage" of B. anthracis by immune rabbits merits serious attention.

If in the interpretation of our experiments with destruction of immunity in rabbits under the influence of trauma we spoke conjecturally about the participation of the nervous system in immunity in anthrax, then on the

basis of the data here presented we can declare about it fully convincingly. True, there is an extensive literature on the role of the nervous system in the pathogenesis of infectious diseases. The investigations of the students of academician A. D. Sepranskii have demonstrated this in a number of infectious diseases. But the researches on the role of the nervous system in immunity are still limited to only the problems concerning the influence of the nervous system on the formation of antigens and not to the test of immune animals for survivability through their controlled infection with fatal doses of the virus.

The direct experiments on the role of the nervous system in immunity, not only in anthrax but also in other infectious diseases, we could not find in the literature accessible to us.

The experiments here cited point to the significance of the nervous system in immunity in anthrax.

Whereas our experiments in vaccination with the formalinized culture of the agent of anthrax (communications I and II) showed that we can effect the mechanism of development of immunity in anthrax through the controlled modification of the reactivity of the organism to the vaccinal preparations, the data here cited attest to the fact that in the appropriate action on the nervous system the reactivity of the organism as a whole is modified, in consequence of which the immune status of the rabbits, vaccinated against anthrax, is destroyed for a period of time.

The investigations in this direction must be expanded because they

will permit us to decipher in greater detail the pathogenesis and interconnection of individual mechanisms of the immunity and their mutual dependence, while the generalization of these data will enable us to struggle more effectively against infectious diseases.